PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US2004/041154	08.12.2004	09.12.2003

International Patent Classification (IPC) or both national classification and IPC
A61P25/04, A61K9/24, A61K9/56

Applicant
EURO-CELTIQUE S.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

   ☐ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☐ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☐ contained in the international application as filed.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 29,64,65

because:

☒ the said international application, or the said claims Nos. 29,64,65 relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-65
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-65
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-28,30-63
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III.

Claims 29, 64 and 65 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of this claim (Article 34(4)(a)(I) PCT).

Re Item V.

1 Reference is made to the following documents:
D1: WO 2004/026283 A (ALPHARMA, INC; BOEHM, GARTH) 1 April 2004
D2: WO 2004/093819 A (EURO-CELTIQUE, S.A) 4 November 2004
D3 : US 2003/157168 A1 (BREDER CHRISTOPHER ET AL) 21 August 2003
D4 : US 2003/124185 A1 (OSHLACK BENJAMIN ET AL) 3 July 2003

2. The state of the art discloses extruded abuse-resistant dosage forms comprising an active agent such as opioids and an antagonist thereof, the latter being optionally in a substantially non-releasable form, i.e. a sequestered form.

2.1 D3 discloses the separate preparation of coated antagonist particles (cf. paragraph [0123]) and of an agonist comprising extrudate which is cut into particles (cf. paragraph [0203]-[0204]). The coated antagonist particles and the extruded agonist particles are subsequently combined in a appropriate dosage form, such as a capsule or tablet (cf. paragraph [0207]-[0208]). Co-extrusion of a core material comprising the antagonist and a shell material comprising the agonist is however not disclosed nor suggested by D3.

2.2 D4 discloses the extrusion of a homogeneous mixture comprising an opioid agonist, an opioid antagonist and a sustained release and binder material (cf. paragraph [0136]-[0137]). D4 also suggests the separate extrusion of the agonist and antagonist and their subsequent combination in form of multiparticulate material in a capsule or tablet (cf. paragraph [0138]). Co-extrusion of a core material comprising

the antagonist and a shell material comprising the agonist is however not disclosed nor suggested by D4.

3. Documents D1 and D2 are referred to by virtue of Rule 64(3) PCT and accordingly are not considered part of the prior art for the purposes of Article 33(2) and (3) PCT.

3.1 D1 (cf. paragraph [0075]) suggests co-extrusion of a material comprising the agonist and of a material comprising the antagonist in sequestered form. Co-extrusion in form of an antagonist-core and agonist shell is however not disclosed.

3.2 D2 discloses co-extrusion of an antagonist core material surrounded by a hydrophobic shell in order to provide sequestered antagonist particles, which are subsequently combined with agonist particles. Co-extrusion of antagonist and agonist is not disclosed.

4. The problem to be solved by the present invention was to provide a co-extruded dosage form comprising an active agent and an adverse agent rendering said dosage form resistant against abusive use. The present invention provides an alternative to the state of the art, which is easily prepared and tamper resistant. The dosage form and method according to claims 1-65 is not disclosed nor suggested by any of the above mentioned prior art documents on its own, nor by a combination of the teaching of said documents. Hence, the subject-matter of claims 1-65 is considered to meet the requirements of novelty and inventive step (Art. 33(2)-(3) PCT).

5. The subject-matter of claims 1-28 and 30-63 is considered to be industrially applicable and accordingly meets the requirements of Art.33(4) PCT.